REMARKS

Reconsideration of this application is requested.

Claims 21 through 24 have been rejected under 35 USC 112, first paragraph, on the ground that the disclosure is enabling only for claims limited to monomorphic essentially full sequence factor IX proteins. In addition, the claims have been rejected under 35 USC 103 as being unpatentable over Suomela or Osterud when taken in view of Schwinn. In this latter regard, the reference to claims 1, 10 through 12 and 14 through 25 in paragraph 18 on page 2 of the action is clearly incorrect. It is assumed that the Examiner intended to refer to claims 21 through 24.

In response to the outstanding rejections, all of the claims in this application have been cancelled and replaced by new claims 25 through 28. Those claims are believed to obviate the outstanding formal rejection, and are also believed to define subject matter which is clearly patentably distinguished over the cited art. Withdrawal of all of the outstanding rejections is therefore respectfully requested.

Referring to the formal rejection, new claims 25 and 27 do not include the language "or of a protein retaining the monomorphism of the cDNA allele and sufficiently similar thereto...factor IX sufficiency" appearing in section (2) of previous claims 21 and 23. Instead, in section (2) of new claims 25 and 27, the claimed protein is defined as having essentially

the amino acid sequence of native human factor IX protein and retaining the monomorphism of the cDNA allele.

It is believed some clarification is required in light of the Examiner's comments on pages 1 and 2 of the Action regarding the recited 90% activity level. This level of activity is not to be understood as an indication of the level of deletion and/or modification which may be effected in the protein sequence to achieve the desired activity level. Rather, the at least 90% activity level range is recited because of the importance of establishing that the product is predominantly fully biologically active factor IX with less than 10% by weight precursor of factor IX protein.

Withdrawal of the outstanding formal rejection is now believed to be in order. Such action is requested.

Turning to the obviousness rejection, it is believed that the claimed factor IX material would not have been obvious to a person of ordinary skill in the art in view of the teachings of the references relied on by the Examiner. The following reasons are presented.

Of the references relied on by the Examiner, Suomela is the only serious attempt to achieve high purification of factor IX. However, the product is obviously not free from all plasma constituents, as evidenced by the fact that gel 4 in Figure 3 on page 150 is not completely free of high molecular weight material towards the top of the band. In isoelectric focusing (Fig. 4), the peak is unsymmetrical (Fig. 4A) or split (Fig.

4B), indicating the presence of impurity. In addition, there is apparently impurity affecting the terminal amino acid, which was indicated to be only 95% tyrosine by N-analysis (see page 149, right hand column near the top). Since even the highly purified product of Suomela is contaminated, it is clear that the less purified products of the other references relied on by the Examiner must be even more contaminated. Thus, Osterud describes a crude purification method based on chromatography on a heparin column and Schwinn describes the procedure in which a crude concentrated plasma is heated with a calcium salt, glycine and sucrose to remove hepatitis viruses. No attempt is made to remove other plasma constituents. In view of this, it is believed that a person of ordinary skill would not have contemplated adopting the Schwinn approach to take the Suomela purification approach any further. Withdrawal of the obviousness rejection on this ground alone is therefore believed to be in order, and this is requested.

Evidence of non-obviousness of the claimed invention is further established by the three executed declarations in the record of this case, one by Professor Brownlee and the other two by independent experts, Dr. Tuddenham and Dr. Gitschier.

Referring, first, to the Brownlee declaration, it is there indicated that he had poor expectations of success in research which ultimately led to this invention. The reasons for those poor expectations lay in (1) the nature of the modifications which the factor IX precursor must undergo after translation and

(2) the fact that tissue cells rather than live animals had to be used for the research. Professor Brownlee indicates that he was particularly doubtful about achieving the beta-hydroxylation (in any kind of cells) and about whether gamma-carboxylation would be achieved in tissue cells. A particularly telling point made by Professor Brownlee is that although a cell line H4-11-E-c3 known to secrete prothrombin was chosen, it did not necessarily follow (1) that this cell line would be capable of the gamma-carboxylation required in the modification of factor IX precursor or (2) that it could carry out beta-hydroxylation. Although it was known that prothrombin requires gamma-carboxylation by a carboxylase dependent on vitamin K, quantitative information was lacking. More importantly, the beta-hydroxylation believed required to modify the factor IX precursor is not a reaction which was believed required to modify prothrombin. In light of Professor Brownlee's evidence, it is clear that a person of ordinary skill in this art would not have expected success in the attempt to produce fully biologically active factor IX protein.

Dr. Tuddenham in his declaration refers to the complications of the post-translation or modification. He mentions that he regarded the research leading to this invention as "highly speculative".

The declaration of Dr. Gitschier is also telling on this point. Dr. Gitschier states in his declaration that he believed that success was by no means assured.

In the outstanding action, the Examiner has commented on the Brownlee declaration indicating, in effect, that that declaration is sufficient to justify withdrawal of the rejections based on anticipation but not sufficient to justify withdrawal of the obviousness rejections. The monomorphism feature is clearly a distinguishing factor which differentiates the claimed protein of the present application from factor IX protein obtained from blood. However, the non-obviousness argument does not rely solely on this feature. In this regard, the Examiner's attention is directed to the attached photocopy of the sequence of factor IX mRNA and its encoded protein. This photocopy is taken from the article by Anson et al (reference AR of record in this case and mentioned several times in the application). Inspection of that photocopy reveals the extreme complexity of the molecules involved. The Examiner's attention is directed, in particular, to the fact that in moving from the directly translated precursor protein to the native biologically active material it is necessary to make post translational modifications at several sites (these are shown in the figure by symbols explained in the legend). While once the mRNA sequence is known, it may be relatively straightforward to genetically engineer the direct exact translation of the mRNA bases into an amino acid sequence, it is certainly <u>not</u> straightfoward to translate <u>and</u> modify to the extent necessary to obtain biologically active factor IX protein from tne mRNA template via cDNA. As is evident from the declaration evidence in this case,

it was not at all obvious this it would be possible or even worth attempting. Surprisingly, however, the inventors of the present application succeeded and found that a biologically active factor IX protein could be obtained by recombinant DNA techniques.

With reference to the points discussed by the Examiner in the paragraph bridging pages 4 and 5 of the action, the Examiner has argued that a person of ordinary skill would have recognized that the safety of the compositions was a necessary prerequisite to their use in humans and would have practised the process of Schwinn until reasonably assured of the safety of the factor IX composition. In response to the Examiner's point, it is noted that it is impossible to ensure absolute safety of a factor IX protein product derived from blood even if extensive purification is carried out. The risk of HIV contamination is still present. Clearly, the presence of even traces of human constituents is extremely relevant.

The Examiner relies on Schwinn as teaching procedures for removing the threat of the presence of blood derived contaminants and thus providing a means for eliminating the alleged problems of the prior art. However, it is to be noted that the Schwinn patent is directed to making a "virtually hepatitis-safe" product" (see the wording of the abstract in claim 1). A factor IX product that is merely "virtually hepatitis-safe" is simply not acceptable to overcome the hazards of blood transfusion. Hepatitis, while serious, is not

necessarily fatal. On the other hand, a trace contamination by the HIV virus causing AIDS is likely to be fatal to a recipient. The fact is that the factor IX product cannot be merely "virtually safe". It is must be "completely safe". This can only be achieved by a product which has not been directly derived from a human source. Furthermore, there is no evidence to suggest that the purification methods suggested by Schwinn for counteracting the problems of hepatitis will necessarily remove the risk of contamination by other viruses such as HIV.

In order to further emphasize the problem of purification, attached is a copy of a recently published paper to Jallat et al, EMBO J., Vol. 9, No. 10, 1990, 3295-3301. In this paper, it will be noted, in the introduction, that high risks are involved in the use of pooled plasma. Thus, it is stated, at page 3295 left hand column, that:

> "Patients are currently treated with pooled plasma concentrates and are at a high risk of possible viral infection." (Emphasis added)

The references relied on by the Examiner (Suomela, Osterud and Schwinn) are all relatively early - Suomela dates from 1976, Osterud from 1978 and Schwinn from 1983. If the Examiner's contention was correct, namely that it would have been obvious to a person of ordinary skill to practice the Schwinn approach "until reasonably assured of the safety of the factor IX composition", then it is not understood why some 7 years later,

Jallat et al are still highlighting the dangers of pooled plasma. Moreover, work continues to develop virus-free factor IX protein which presumably would not be occurring if the Examiner's contention regarding Schwinn were correct. Similarly, haemophiliacs continue to be subjected to the risk of contracting HIV through blood transfusions, which also would not be the case if the Examiner's position were correct.

The invention as claimed in the present application is therefore clearly patentably distinguished over the cited teachings. Withdrawal of the outstanding obviousness rejection is respectfully requested.

In the circumstances, it is believed that this application is now in a form suitable for immediate allowance, and early action to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:mss
2200 Clarendon Boulevard
14th Floor
Arlington, Virginia 22201
703/875-0400
Attachments: Sequence from Anson et al and Jallat et al reference

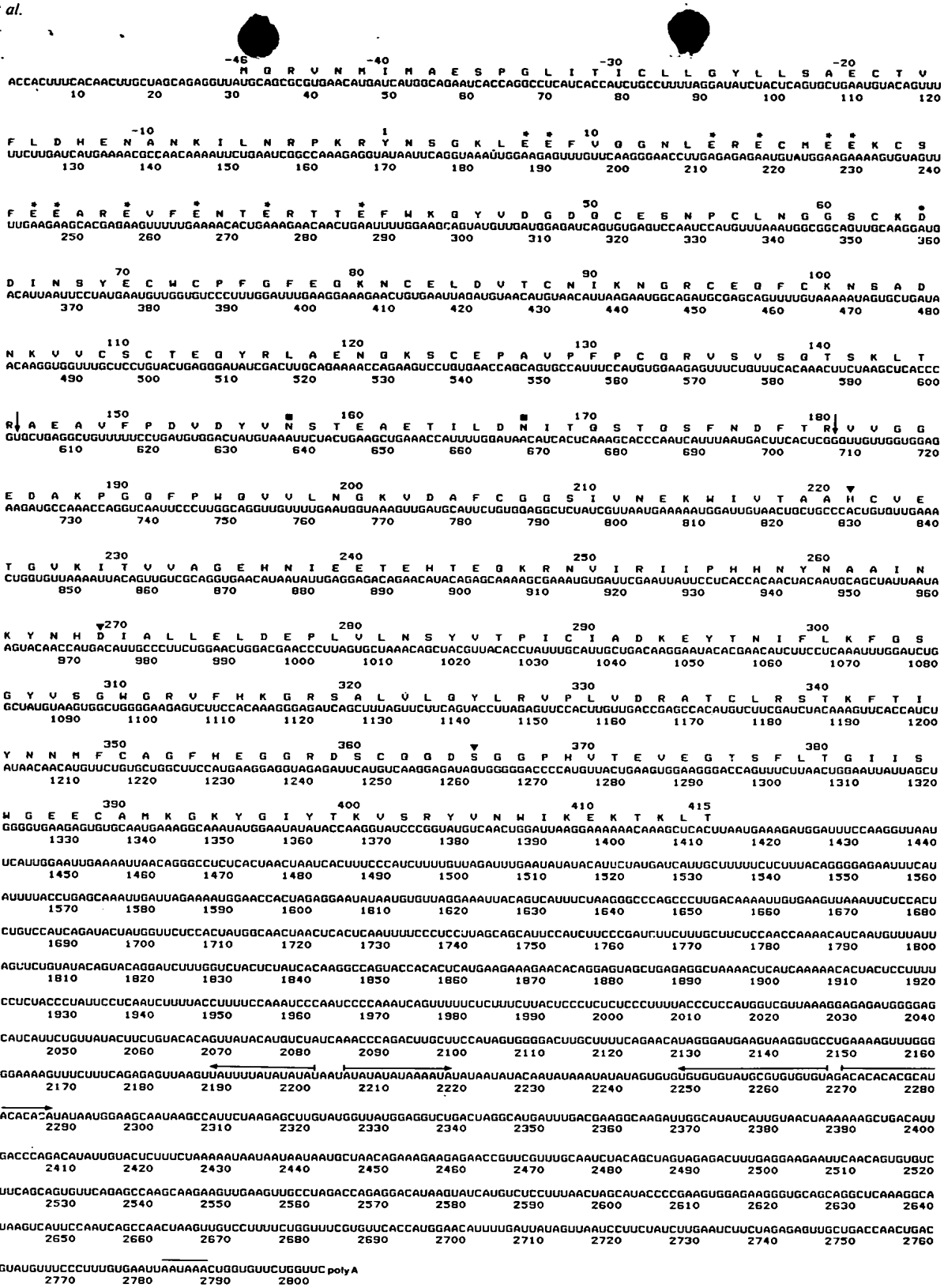

Fig. 2. Sequence of factor IX mRNA and its encoded protein. The symbols 1 – 415 define the mature protein and −46 to −1 the precursor region. The latter may be further subdivided into a hydrophobic signal region −46 to −21, and a hydrophilic precursor region −20 to −1 containing three basic amino acids between residues −4 to −1. Vertical arrows indicate the peptide bonds cleaved during activation in clotting. Post-translational modifications are marked (* = 12 γ-carboxyglutamyl residues, ● = β-hydroxyaspartyl and ■ = two Asn-linked carbohydrate residues). The AAUAAA consensus sequence is overlined. His (221), Asp (269) and Ser (365) are marked (▼). Local potential hairpin loops are shown by horizontal arrows.